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Ethnopharmacological and Phytochemical Studies of Tridax Procumbens Linn: A Popular Herb in Ayurveda Medicine

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***Abstract*:- *Tridax procumbens* (*T. procumbens*) Linn. is a medicinal plant found in tropical, sub-tropical and mild temperate regions around the world being used in Ayurveda treatment for liver disorders, boils, blisters, cuts, wound healing and as an anticoagulant, antifungal, and insect repellent. The plant is known to contain flavonoids, alkaloids, carotenoids, hydroxycinnamates, lignans, benzoic acid derivatives, phytosterols and tannins. The plant is also associated with endophytes to produce secondary metabolies by endophytes possessing antibacterial and antifungal activities. Different parts of this plant and essential oil are associated with ethnopharmacological properties like wound healing, antibacterial, immunomodulation, antiinflammatory, antidiabetic, vasorelaxant, antihyperlipidemic, anticancer, antiplasmodial, anticoagulation and antihepatic. Most of these studies validate the concept of earlier claims that T. procumbens's potential as a medicinal plant. Further studies are required to unravel other pharmacological activities as well as the target-based mechanism of actions. The review also highlights the need for exploring lead molecules from these myriad of compounds that are of vital importance in drug discovery strategies.**

Keywords: Tridax procumbens, Wound healing, Antiinflammatory, Immunomodulatory, Metabolic syndrome, Cancer, Hepatoprotection, Antiparasitic, Antibacterial, Bone homeostasis modulators.

1. INTRODUCTION

T. procumbens Linn., though a native of tropical America is also found in India, tropical Africa, Asia, Australia and India as a creeper weed. *T. procumbens* has been traditionally used in Ayurveda system for centuries and possesses different pharmacological properties including wound healing, anti-oxidant, antibacterial, antifungal, immunomodulatory, antiinflammatory, antidiabetic, vasorelaxant, antihyperlipidemic, analgesic, antiplasmodial, anticoagulation and antihepatic [1]. The diverse biological activities are due to various phytochemicals present in the plant. The aim of this review is to critically evaluate *T. procumbens* as an important medicinal plant with emphasis on the *in-vivo* properties of the phytochemicals and their roles in signalling pathways that can be manipulated for specific pharmacological actions

2. METHODS

For the review, articles were extracted in Pubmed Central search engine using the key word *Tridax Procumbens*. In addition, phytochemicals, pharmacology, clinical trials, Flavanoids, Kaempferol, Catechins, alkaloids, antidiabetic, anti-inflammatory, immunomodulatory, antimicrobial, hepatoprotection, antiparasitic and bone homeostasis were also added to the search window to extract all relevant articles pertaining to *Tridax Procumbens*.

3. BOTANICAL DESCRIPTION

The taxonomical classification of *T. procumbens* L. is shown in Table 1.

International Journal of Engineering Research & Technology (IJERT)
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Kingdom	Plantae
Sub-Kingdom	Tracheobionta
Division	Spermatophyte
Sub-division	Magnoliophyta
Class	Magnoliopsida
Sub-class	Asteridae
Order	Asterales
Family	Araceastee
Genus	Tridax
Species	procumbene

Table 1. Taxonomic classification of *T. procumbens* L.

The plant has an average height of around 20-60 cm and is branched. Leaves are 4-8 cm long, simple, opposite and stipulate. Inflorescence is around 12-32 cm, oval shaped and held by peduncle, with ray florets and disc florets. Flowers are daisy like with yellow centred white or yellow petals. Numerous, tubular disc florets are surrounded by a ring of short, strap-shaped ray florets. Fruit is cypsela, black or brown in colour at maturity and surrounded with feathery bristles [2]. The stem is cylindrical and covered with hairs of about 1 mm with tap root system [3]. The registered number of chromosome present in *Tridax* are 36 (2n) [4]. Growth of plant takes place during monsoon season as it requires abundant water for growth and sustenance.

4. PHYTOCHEMICAL CONSTITUENTS

The leaf and other parts of T. *procumbens* L. are reported to have flavonoids, alkaloids, carotenoids, hydroxycinnamates, lignans, benzoic acid derivatives, phytosterols, tannins, crude proteins, crude fiber, soluble carbohydrates and calcium oxide [5]. The presence of fumaric acid, β-sitosterol and the pentacyclic triterpenoid oleanolic acid have also been reported [5]. Luteolin, glucoluteolin, quercetin, and isoquercetin have been reported in flower extracts [6]. Some of the other phytochemicals present abundantly in T. procumbens are 2,6-dihydroxyacetophenone, 2-O-β-D-glucopyranoside, echioidinin, pinostrobin, dihydroechioidinin, tectochrysin-5-glucoside, methyl salicylate glucoside, 5,7,8-trimethoxyflavone, skullcapflavone-2-methyl ether, androechin, tectochrysin, 5,7,2'-trimethoxyflavone, echioidin, skullcapflavone ii, 5,7-dimethoxyflavone and andrographidine [6].

4.1 Flavonoids

A recent study has demonstrated the presence of twenty three flavonoids in *T. procumbens* [7] with total content around 65 g/kg. Kaempferol and catechin and its derivatives (-)-epicatechin, (+)-catechin, (-)-eigallocatechin, (+)-gallocatechin, (-)-epigallocatechin-3-gallate (EGCG) and (-)-epicatechin-3-gallate) account for about 17.59% and 26.3% respectively. The remaining 56.11% represent sixteen flavonoids namely biochanin, apigenin, naringenin, daidzein, quercetin, butein, robinetin, baicalein, nobiletin, genistin, ellagic acid, luteolin, myricetin, baicalin, isorhamnetin and silymarin (Figure 1 and 2) [7].

International Journal of Engineering Research & Technology (IJERT)
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Vol. 9 Issue 09, September-2020

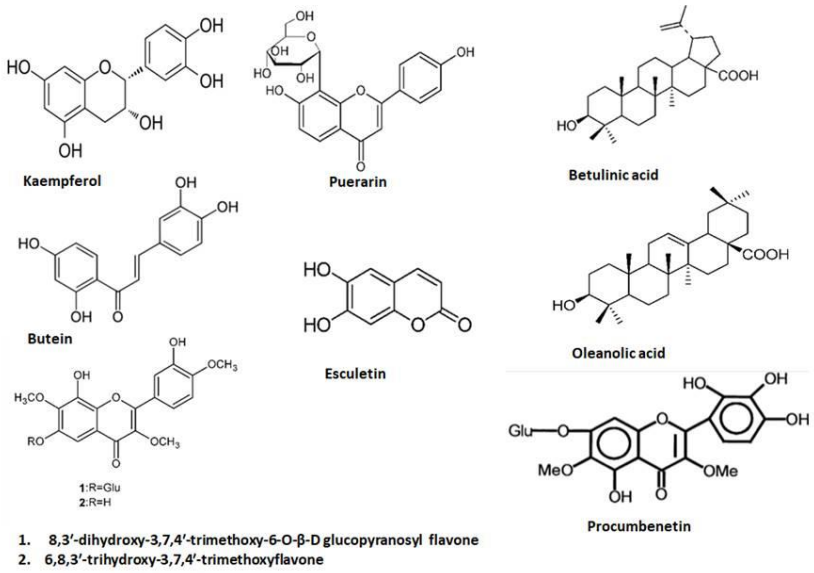

Figure 1. Structures of some flavanoids identified in *T. procumbens*

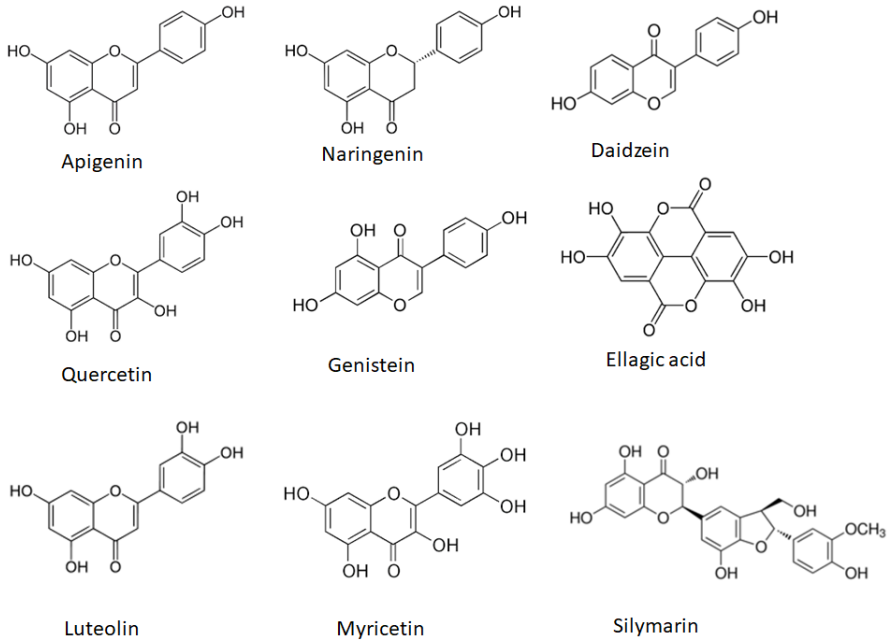

Figure 2. Other flavonoids present in *T. procumbens*

The flavonoids detected in *T. procumbens* are known to mediate pharmacological activities including free radical scavenging, antiinflammatory, antiallergic, antiplatelet aggregation, antimicrobial, antiulcer, antiviral, antitumor and antihepatotoxicity [8]. Two new flavones, 8,3′-dihydroxy-3,7,4′-trimethoxy-6-*O*-*β*-D-glucopyranosylflavone and 6,8,3′-trihydroxy-3,7,4′-trimethoxyflavone were isolated from the whole plant along with four known compounds puerarin, esculetin, oleanolic acid and betulinic acid (Figure 1) exhibiting antioxidant activity [9]. A new flavonoid procumbenetin, from the aerial parts of *T. procumbens*, has been characterized as 3,6-dimethoxy-5,7,2',3',4'-pentahydroxyflavone 7-*O*-β-D-gluco-pyranoside based on spectroscopic techniques and by chemical means [10].

Kaempferol is the main flavonoid found in the leaves of *T. procumbens* L [7], the structure of which is shown in Figure 1. Preclinical studies have shown that kaempferol and its glycosidic derivatives exhibit wide range of medicinal properties such as antioxidant, analgesic, antiinflammatory, antimicrobial, antifungal, anticancer, cardioprotective, neuroprotective, hepatoprotective, antidiabetic, hypocholesterolemic, hypotriglyceridemic, antiosteoporotic, estrogenic/antiestrogenic, anxiolytic and antiallergic activities (11-14). Kaempferol has many beneficial effects on inflammatory diseases by mediating antiinflammatory or immunomodulatory activities. It inhibits various signalling pathways and suppresses matrix degrading enzymes (Table 2).

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Anti-inflammatory Disease	Mode of Action	References
Intervertebral Disc Degeneration (IVD)	Inhibition of lipopolysaccharide(LPS) induced apoptosis, chondrogenic markers (collagen II, SOX-9 and aggrican), matrix degrading enzymes and lipid anabolism associated genes	15
Osteoarthritis	Inhibition of NF-kB signaling pathway	16
Colitis	Inhibition of NF-kB signaling pathway	17
Mastitis	Suppression of myeloperoxidase (MPO), IL-6, TNF- α and ANGPTL2 expression	18
Rheumatoid Arthritis	Inhibition of fibroblast like synoviocytes (FLS) by blocking mitogen activated protein kinase (MAPK) pathway without affecting TNF- α receptors	19
Allergic asthma	Suppression of eosinophil infiltration	20
Mucus Hypersecretion	Disturbance of Transforming growth factor β (TGF-β) and ER stress signaling of inositol requiring enzyme 1α/TNF receptor associated factor 2/c-JuN-terminal kinase (JNK)	21
Gastric Ulcer	Inhibition of neutrophil accumulation, MPO activity and inflammatory cytokines; improves NO production	22

Table 2. Antiinflammatory mechanisms of kaempferol on inflammatory diseases

Studies have shown a positive link between dietary kaempferol and reduction in risk of chronic diseases including cancer [11]. At the molecular level, kaempferol can modulate many important elements in cellular signal transduction pathways in apoptosis, metastasis, angiogenesis and inflammation [15-23]. Epicatechin, exists in (+)-catechin and (-)-epicatechin (cis) forms (Figure 3). (-)-Epicatechin has antioxidant property due to its ability to neutralize reactive oxygen species (ROS) in the cell. It also modulates cell signalling including the mitogen-activated protein kinase pathway involved in cell proliferation [24].

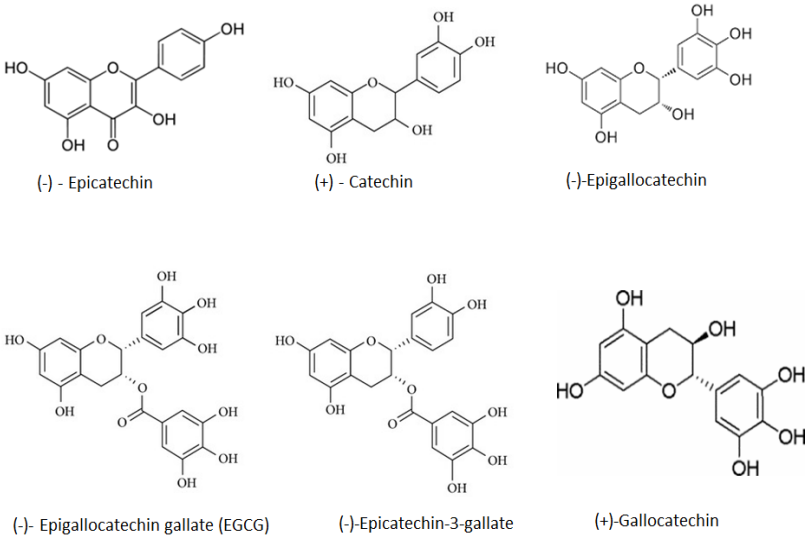

Figure 3. Catechin and its derivatives reported in *T. procumbens*

(+)-Catechin can attenuate inflammatory responses triggered by TNF-α by inhibiting the gene expression of proinflammatory cytokines IL-1α, IL-1β, IL-6, IL-12p35, and inflammatory enzymes like inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX2), and also by enhancing the gene expression of antiinflammatory cytokines including IL-4 and IL-10. (+)-Catechin also inhibits the activation of inflammatory signalling mediated by nuclear factor (NF-κB), AMP activated protein kinase (AMPK), forkhead box O3a (FOXO3a) and sirtuin1 (SIRT1) [25]. Inflammation is considered a central component of allergies and considered life threatening during conditions like anaphylactic shock [26]. Reports have suggested the pharmacological effects of (−)-epicatechin during allergic immune response. When ovalbumin-challenged mice were fed with pellets containing 1%, 0.3%, or 0.01% purified (−)-epicatechin for 8 days, reduction in clinical symptoms were reported including scratching around the nose or head, diarrhoea, together with reduction in ovalbumin-specific IgE levels [27]. Studies

International Journal of Engineering Research & Technology (IJERT)
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Vol. 9 Issue 09, September-2020

have shown that EGCG, a derivative of catechin can reduce the effects of food allergen ovalbumin by interacting with its secondary β sheet structure thereby preventing uptake by antigen presenting cells [28].

4.2 Alkaloids

A recent study by Ikewuchi *et al* demonstrated that the total alkaloid content in the leaves of *T. procumbens* L were 102.421 g/kg and 10.191 g/kg of dry and wet weight respectively (Fig. 4).

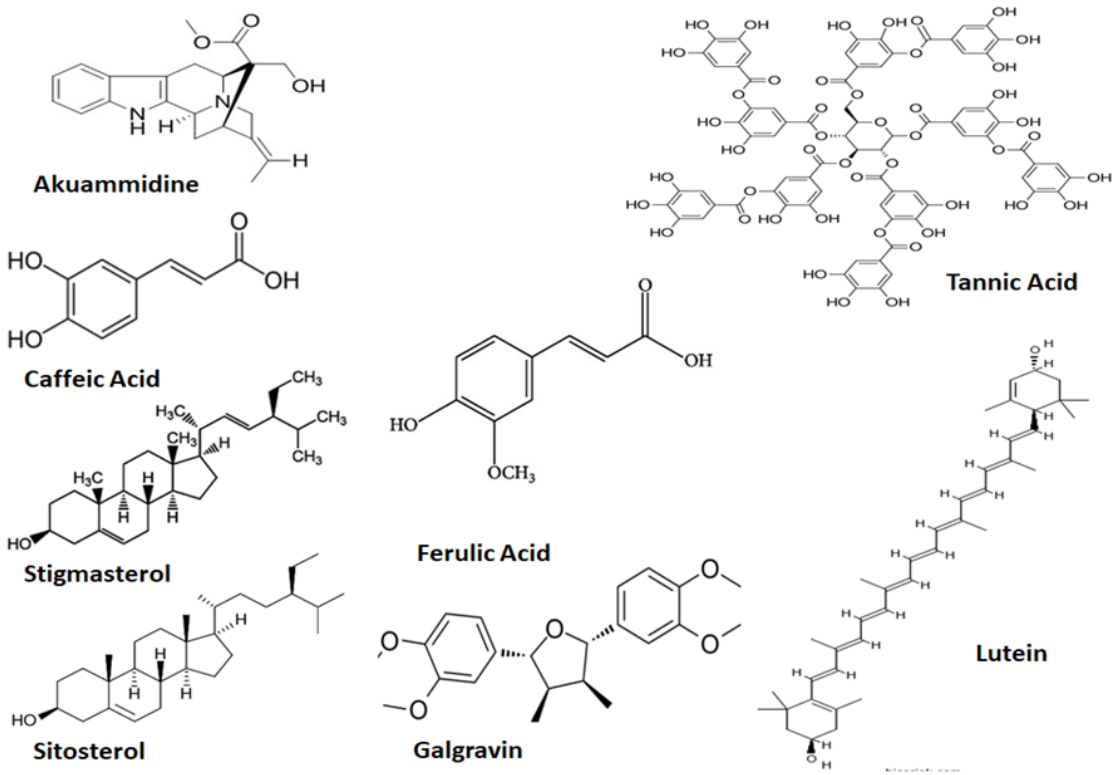

Figure 4. Other phytochemicals present in *T. procumbens*

Akuammidine is known to have biological activities such as antibacterial, antifungal, antimalarial, antiinflammatory, hypotensive, skeletal muscle relaxant, local analgesic and anti-depressant [7]. Other studies also confirmed the presence of different alkaloids in the leaves of *T. procumbens* L [29,30]. These alkaloids have been isolated using different solvents like chloroform and methanol and using different methods such as infused and decoction in a qualitative manner [29,30].

4.3 Other phytochemicals

The other bioactive molecules in the leaves of *T. procumbens* include caffeic acid, ferulic acid, tannins, stigmasterol and lutein [7, 29, 30]. *In vitro* studies have shown that caffeic acid and ferulic acid have antioxidant, antiinflammatory, anticancer and antimicrobial activities [31, 32]. Tannic acid and other hydrolysable tannins have multiple health benefits including reduced risk of cardiovascular disease, anticancer, antidiarrheal, antiobesity, antibacterial, antiviral, antifibrotic and neuroprotection [33,34]. One of the molecular mechanisms attributed to tannin's health benefits is the inhibition of Ca^{2+} -activated Cl^- channels [34]. Stigmasterol has pharmacological activities such as antiosteoarthritic, antihypercholestrolemic, cytotoxicity, antitumor, hypoglycaemic, antimutagenic, antioxidant, antiinflammatory and analgesic [35]. Lutein, a type of xanthophyll carotenoid has beneficial effects against age-related macular degeneration (AMD), age-related cataract (ARC), ischemic/hypoxia induced retinopathy, light damage of the retina, retinitis pigmentosa, retinal detachment, uveitis and diabetic retinopathy [36], lung and breast cancers, heart disease and stroke [37].

5. PHARMACOLOGICAL PROFILE OF *T. PROCUMBENS*

5.1 Wound healing activity

Traditionally, the juice from leaves of *T. procumbens* has been used for healing dermal wounds. Wound healing process involves three phases namely inflammation, angiogenesis and collagen deposition. In an excision and incision wound model in Wistar rats, both aqueous and ethanolic extracts of *T. procumbens* increased the tensile strength of the wound compared to control rats. Further, wound healing biomarkers such as hydroxyproline, collagen and hexosamine were significantly increased [38]. The wound healing ability was also confirmed by topical ointment formulation of the leaf extract of *T. procumbens* in a mouse model, where dose-dependent improvement of cell proliferation and wound remodelling was observed [39]. Lysyl oxidases (LOX) are a group of enzymes catalyzing cross-linking reaction of collagen and elastin to form covalently linked,

International Journal of Engineering Research & Technology (IJERT)
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Vol. 9 Issue 09, September-2020

insolubilize extracellular matrix (ECM) proteins thereby facilitating ECM stabilization through ECM formation, development, maturation and remodelling [40]. The increased lysyl oxidase activity on treatment with *T. procumbens* extract in rat wound healing model suggests their role in wound healing [41]. In *C. elegans* wound model and cell lines scratch wound healing assay, the wound healing ability of *T. procumbens* and its phytocompounds Octa decenoic acid (ODA), Pyridine carboxamide oxime, known as Nicotinamide (NA) and Dimethyl Benz[c]acridine (DMB) were studied. Results indicated that the wound healing ability was mainly contributed by NA in the chloromethyl nicotinamide derivative form by interacting with the wound healing biomarker, glycogen synthase kinase 3 (GSK-3) [42].

5.2 Antiinflammatory Activities

Since, inflammation is one of the three phases of wound healing, *T. procumbens* was evaluated for its antiinflammatory potential. An earlier study showed that aqueous extract of *T. procumbens* exhibited a dose dependant inhibition of paw volume in carrageenan induced rat paw edema and cotton pellet granuloma model as well as significant reduction in cell migration compared to control [43]. In another study, *T. procumbens* was shown to possess dose dependent analgesic activities in formalin, acetic acid and complete Freund's adjuvant (CFA)-induced pain models. These protective actions against pain may be attributed to flavonoids and sterols present in the extract and have the potential to develop effective analgesics [44]. The antiinflammatory activities of *T. procumbens* were further corroborated in an *in vivo* carrageenan-induced rat paw edema model in which standardized EtOAc, MeOH and 70% EtOH extracts of *T. procumbens* aerial parts displayed anti-inflammatory potential at a median dose of 200 mg/kg with maximum activity by EtOH fraction comparable to the control ibubrufen at 100 mg/kg (% inhibition of paw edema at 5 h: 41.2 ± 2.2 vs. 52.2 ± 1.5) [45]. The EtOAc extract exhibited strong antioxidant activity against 1,1- diphenyl-2-picrylhydrazyl (DPPH) and 2,2′-azino-bis (3-ethylbenzthiazoline-6-sulfonic acid) (ABTS) free radicals and COX1 (Cyclooxygenase 1) and COX2 (Cyclooxygenase 2) inhibitory activities compared to MeOH and 70% EtOH extracts which may be attributed to the flavonoids and other polyphenols present in the extracts [45]. In a similar study, antiinflammatory activities were demonstrated in carrageenan induced mouse model where improved inflammation in histopathological scoring of mice paw, decreased gene expression of TNF-α and COX2 in mouse paw treated with EtOH extract of *T. procumbens* were observed compared to control [46].

5.3 Immunomodulatory Activities

The ability of bioactives in modulating immune response to ameliorate certain diseases reflects its biological or pharmacological effects on humoral or cellular immune response [47]. Intraperitoneal injection of an aqueous extract of *T. procumbens* Linn. (TPEIF) in Swiss male albino mice exhibited significant increase in immunomodulatory indexes such as phagocytic index, leucocyte count, splenic antibody secreting cells and augmentation of both humoral and cellular immune response as evidenced by elevation of heamagglutination antibody titer and delayed type hypersensitivity reaction respectively [48]. Further, the aqueous extract protected against anaphylactic shock in mice sensitized with 1 mg bovine serum albumin with reduction in number of animals presenting anaphylactic symptoms. The overall immunomodulatory responses may be due to the presence of the sesquiterpene and terpenoids in the aqueous extract. The detection of a specific antibody to tetanus toxoid (TT) in TPEIF treated animals showed significant stimulation of specific antibodies against TT suggesting a role for aqueous extract of *T. procumbens* Linn. in immuno-compromised patients and as a vaccination adjuvant to reduce the number of non-responders to vaccines [48]. In another study, oral administration of methanol extract, chloroform fraction (CFTP), ethyl acetate fraction (EFTP), n-Butanol fraction (NFTP) and remnant water soluble fraction (RWSFTP) fractions in Swiss Albino Mice (20-40 mg/kg body weight) exhibited positive response in stimulating immune responses. Notably, EFTP and NFTP fractions rich in flavonoids and triterpenoidal saponin modulated both cell mediated and humoral components of the immune system [49]. Furthermore, ethanolic extract of *T. procumbens* stimulated humoral response in Swiss albino Rats and phagocytosis and also conferred protection against *Pseudomonas aeruginosa* infection [50].

5.4 Antimicrobial Activity

Bioactives from plants are used in traditional therapies as antimicrobials [51]. Aqueous extracts from different plants including *T. procumbens* possess antimicrobial activities [52,53]. *T. procumbens* extract exhibited antibacterial activity against clinically relevant Gram positive and Gram negative bacteria [54-58]. In one study, *T. procumbens* crude extract of n-hexane was active against pathogens like *Mycobacterium smegmatis*, *Klebsiella* species and *Salmolella* species whereas ethyl acetate extract was active against *Mycobacterium smegmatis and S. aureus*. These differential antibacterial activities may be due to the presence of mixture of hydrocarbons in n-hexane extracts such as neophytadiene and long chain fatty acids such as hexadecanoic acid. In the case of ethylacetate extract, fatty acids, aromatic compounds, polyaromatic carboxylic acids, polysubstituted phenols and thiols were reported [54]. *T. procumbens* leaves extracted in different solvents exhibited antibacterial activities. Chloroform extract was effective against *B. faecalis* and *E. coli*, the ethanolic extract was moderately active against *B. faecalis* whereas petroleum ether extract was active against *B. faecalis*. This study suggested that tannins in chloroform extract and alkaloids in petroleum ether and ethanol extracts were responsible for the antimicrobial activities [55]. Though, the ethanolic extracts of *T. procumbens* were reported to have antibacterial activity by many researchers [55,56], Saritha *et* al. have reported no antibacterial activity in whole plant extract which could be due to lower concentration of the actives [57]. Methanolic leaf extract of *T. procumbens* from one study inhibited *S. aureus* causing bovine mastitis [58] suggesting that there is wide range of antibacterial activities possessed by this plant. Efforts were also made to prepare nanoparticles from the leaf of *T. procumbens*.

International Journal of Engineering Research & Technology (IJERT)
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Vol. 9 Issue 09, September-2020

The silver nanoparticles prepared from the callous extracts of stem and leaf of the plant exhibited some activity against *E. coli*, *V. cholerae*, *A. niger*, and *A flavus* [59] and Cu_2O nanoparticles [60] against *E. coli*. More investigations are needed to improve this technology.

It has been documented that endophytic microorganisms including fungi or bacteria results in the production of antifungals such as pseudomycins, ecomycins [61,62] and antibacterials such as indolosesquiterpenes compounds [63]. Fungal or bacterial endophytes (BEs) are considered as potential sources of novel antibiotics. In a recent study, improvement of experimentally induced dermatophytic lesions by *T. procumbens* plant extract suggests the presence of antifungal principle to cure dermatophytosis [64]. Further, the plant is also known for its antibacterial properties [65, 66]. Analysis of fifty novel endophytes from the leaves and stems of *T. procumbens* revealed the association of *Bacillus* spp., *Cronobacter sakazakii*, *Enterobacter* spp., *Lysinibacillus sphaericus*, *Pantoea* spp., *Pseudomonas* spp. and *Terribacillus saccharophilus* with the plant [67]. Bacterial endophytes associated with roots of *T. procumbens* can be used for bioremediation of heavy metals [68]. Fungal endophytes in association with *T. procumbens* have been reported to have antibacterial activity. In an experimental study, out of six endophytic fungi (TP-1 to TP-6) isolated from the leaves of the *T. procumbens*, TP-1 identified as *Alternaria* sp. exhibited maximum antibacterial activity against *Escherichia coli*, *Salmonella Typhi*, *Bacillus sp.*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *klebsiella pneumonia* [69].

5.5 Life Style Diseases and T. procumbens

Metabolic syndrome (MetS) is a cluster of metabolic abnormalities having three of five clinical criteria: obesity, dyslipidemia, low serum HDL cholesterol, hypertension and hyperglycemia [70]. Genetic factors, acquired factors, sedentary life style and dysregulated endocrine signalling are primary contributors of MetS [71]. As per American Heart Association (AHA), treatment involves multiple pharmacological interventions to adequately correct the individual risk factors [72]. Natural products are important source of therapeutically effective drugs with more than 80% of world's population depending on plants [73]. FDA (Food and Drug Administration)-approved drugs has revealed that derivatives of natural products represent one-third of the total approved New Molecular Entities (NMEs) of which 50% are from mammals, 25% each from microbes and plants [74].

The antidiabetic activities of *T. procumbens* were documented in various animal models [75-78]. Oral administration of whole plant methanolic extract of *T. procumbens* in alloxan-induced diabetic rats showed a significant decline in fasting blood glucose without much effect on body weight reduction and toxicity [75]. Antidiabetic activity was reported when another aqueous and alcoholic extracts of the leaves of *T. procumbens* were tested in alloxan-induced diabetic rats [76]. Administration of ethanolic extract of *T. procumbens* (whole plant) at 250 and 500 mg/kg in streptozotocin-nicotinamide induced Wistar rats have demonstrated significant reduction of blood glucose, serum cholesterol, triglycerides, and LDL- cholesterol compared to the standard anti-diabetic drug glibenclamide at 0.25 mg/kg. Other favourable pharmacological profiles such as increased HDL-cholesterol and body weight reduction indicated that standardized extracts of *T. procumbens* alone or in combination with other herbal extracts may be an excellent choices to treat MetS [77,78]. Polyherbal formulation may bring additive or synergic effects in their pharmacological responses against MetS which were not explained [78]. Ali *et al* [79] reported that oleanoic acid and its derivatives are inhibitors of α-glucosidase with IC_{50} as low as 7.97 ± 0.214 µM. Inhibition of α-glucosidase slows the breakdown of carbohydrate, enhances its utilization, lowers insulin levels and maintains glucose homeostasis. In one study, ether, methanol, and chloroform extracts of *T. procumbens* exhibited a significant reduction of α-glucosidase which may be due to oleanoic acid derivatives [79,80]. In a clinical study, when aqueous whole plant *T. procumbens* extract was administered for 4 weeks along with prescribed medications to type 2 diabetics, significant lowering of fasting and postprandial blood glucose was observed [81].

Since hypertension (50-75%) and obesity (30-50%) are co-morbid conditions in type 2 diabetics [82], phytotherapeutic intervention is ideal to treat more than one condition of MetS. When 20 mg/kg of *N*-nitro-L-arginine methyl ester (L-NAME)-induced hypertension rats were treated with aerial parts of *T. procumbens* extracts prepared in different solvents (cyclohexane, micellar, dichloromethane and ethyl acetate) for seven days, ethyl acetate and dichloromethane fractions were most effective in lowering the mean arterial pressure of rats comparable to the standard ACE inhibitor captopril. The hypotensive effects of these fractions may be due to the enriched alkaloids and flavonoids and the probable vasorelaxation effect of flavanoids [83]. The mechanisms of vasodilation of *T. procumbens* extract include blocking or modulating cGMP and cAMP in rat aorta artery [84], blocking Ca^{2+} channels, stimulation of prostacyclin production and opening of small-conductance Ca^{2+} activated potassium channels in rat superior mesenteric arteries [85] and by the release of NO from endothelium of rat smooth muscle [86].

5.6 Anticancer Activity

T. procumbens flower crude aqueous and acetone extracts when tested against prostate epithelial cancerous cells PC3 in MTT assay, the former demonstrated anti-cancer activity [87]. Sankaranarayanan S. *et al.* [88] have isolated a compound Lupeol which inhibited cell viability of human lung cancer cell A-549 in MTT assay upto 90%. Further, this compound at 320 µg/ml concentration showed anti-cancer potential in various assays namely colonogenic survival determination, cell cycle control, cell based assay for inhibition of COX-2 activity and DNA fragmentation analysis [88]. The essential oil of *T. procumbens* L

International Journal of Engineering Research & Technology (IJERT)
ISSN: 2278-0181
Vol. 9 Issue 09, September-2020

significantly prevented B16F-10 cell line-mediated lung metastasis in C57BL/6 mice along with prevention of tumor directed angiogenesis and induction of apoptosis [89]. The crude aqueous extract of *T. procumbens* when nanoformulated with poly (vinyl pyrrolidone) exhibited superior anticancer, antioxidant and antiinflammatory activity suggesting an effective strategy to enhance therapeutic index [90].

5.7 Hepatoprotective Activity

Drug-induced liver injury (DILI) or *drug-induced hepatotoxicity* is caused by all classes of drugs, herbal and dietary supplements. Specific examples of drug classes include anaesthetics (halothane), non-steroidal anti-inflammatory drugs (diclofenac), antibiotics (rifampicin, beta lactam antibiotics such as penicillin and cephalosporin), antifungals (ketoconazole), highly active antiretroviral therapy (HAART), oral hypoglycemics (PPAR-γ agonists like troglitazone, rosiglitazone, sulfonylureas such as glimepiride) and lipid lowering drugs (statins and ezetimibe) [91]. The mechanisms of DILI include inhibition of mitochondrial respiratory chain, increased generation of reactive oxygen species (ROS), ATP depletion, triggered apoptosis and immune mediated injury [91]. Though, the global use of herbal therapy for hepatotoxicity is increasing, evidence suggests that these may also cause hepatotoxicity. For instance, herbal toxicity is reported for Herbalife® products causing differential patterns of liver injury [92]. Thus, phytotherapies to counter hepatotoxicity need a cautious approach.

The oral administration of *T. procumbens* ethanolic extract at 100, 200, 300 and 400mg/kg body weight for the period of 7 days in paracetamol induced hepatotoxic male albino rats, resulted in the significant reversal of increased alanine aminotransferase, aspartate aminotransferase, serum alkaline phosphatase and enhanced lipid peroxidation. Increase in superoxide dismutase and catalase activities in liver cells suggest antioxidant and hepatoprotective efficacy of *T. procumbens* L. [93]. When petroleum ether, methanol and chloroform/water extracts were orally administered in D-galactosamine induced hepatotoxic male Wistar Albino rats, significant reduction of liver enzymes alanine transaminase (ALT) and aspartate transaminase (APT) compared to non-treated control (D-galactosamine treated rats) along with dose dependent antioxidant activities in methanolic extract compared to other fractions [94]. Hepatoprotective effects of *T. procumbens* were also demonstrated against carbon tetrachloride induced liver injury in Wistar rats [95], isoniazid-rifampicin induced toxicity in albino rats [96] and rifampicin induced hepatotoxicity in male Albino rats [97]. Hepatoprotection against experimentally induced hepatitis [98,99] by *T. procumbens* was also reported. Pretreatment of D-galactosamine/Lipopolysaccharide induced-hepatitis in rats with chloroform insoluble fraction from ethanolic extract of *T. procumbens* improved liver parameters like aspartate transaminase, alanine transaminase, alkaline phosphatase, lactate dehydrogenase, γ-glutamyl transferase, bilirubin and lipid levels both in serum [98]. In the same animal model, Ravikumar *et al.* demonstrated the improvement of liver antioxidant defense system such as decreased lipid peroxides, increased activities of superoxide dismutase, catalase, glutathione peroxidase, glutathione-S-transferase and the non-enzymatic antioxidants namely reduced glutathione, vitamin C and vitamin D [99].

5.8 Bone Homeostasis Modulators

Plant-derived flavonoids are shown to function as bone homeostasis modulators by stimulating osteoblasts function and inhibiting osteoclasts functions either alone or in combination [100]. Primary osteoclastic cells when treated with *T. procumbens* fraction (TPF), showed significant suppression of Receptor activator of nuclear factor kappa-B ligand (RANKL)-induced differentiation of osteoclasts and the formation of pits were noticed [101]. The down-regulation of osteoclast differentiation genes like Tartrate resistant acid phosphatase (Trap), Cathepsin K, Matrix metalloprotease-9 (Mmp-9), and Matrix metalloprotease-13 (Mmp-13) and proteins such as Cathepsin K, Mmp-9, and Mmp-13 in primary osteoclast cells treated with TPF suggests that TPF could be a potential anti-bone resorption agent to treat patients with bone loss associated diseases such as osteoporosis [101]. When mice were treated with TPF, bone formation related indices like bone mineral density, bone mineral content, osteoblast number, osteoblast surface, bone volume, mineralizing surface, mineral apposition rate and bone formation rate were significantly increased compared to the control mice [102]. Molecular mechanisms of inhibition of osteoclast differentiation by TPF could be due to the down-regulation of transcription factors such as c-Fos, nuclear factor of activated T cells cytoplasmic 1 (NFATc1) and activator protein-1 (AP-1) [103].

5.9 Antiparasitic Activity

Parasitic infections caused by protozoa, nematodes, trematodes, and cestodes account for more than 30% of the human population and the plant extracts and their secondary metabolites may be an excellent strategy to target these infections [104]. *T. procumbens* extracts have been shown to possess antiparasitic activities against *Leishmania mexicana* [105] and *P. falciparum* [106]. An active bioactive compound (3S)-16,17-didehydrofalcarinol isolated from *T. procumbens* exhibited significant *in vitro* activities against promastigotes and intracellular amastigotes of *L. mexicana* [105]. Oral administration of *L. mexicana*-infected mice with *T. procumbens* extract in combination with *Allium sativum* extract, known for its immunomodulatory effect, exhibited significant protection against infection as evident by improved anti-inflammatory score in mouse footpad assay and Th1-type immune response [107].

6. CONCLUSION

This is a comprehensive review that highlights the various phytochemicals identified in *T. procumbens* together with their diverse pharmacological attributes. Since, most of the small molecules approved by FDA are derived from plant sources, it is essential to evaluate the plant in a systematic manner to identify bioactives which could lead to the discovery and development

International Journal of Engineering Research & Technology (IJERT)
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Vol. 9 Issue 09, September-2020

of new drugs against various ailments. Though, *T. procumbens* has been used in many traditional medicines, scientific data relating their phytochemicals with published pharmacological properties are lacking. Many of the studies have used plant extracts followed by qualitative analysis of its phytochemical constituents. Researchers should try to employ new drug discovery principles like bio-assay guided phytochemical identification, phenotypic screening using relevant cell culture models and if possible demonstrate pharmacokinetic-pharmacodynamic correlation (PK-PD) to show the efficacy of the preparation. Attempts should also be made to identify the active metabolites mediating the *in vivo* efficacy to ensure standardized extract preparation. In addition, a battery of enzyme targets can be identified for different diseases and the partially purified bioactives checked for inhibitors or activators. Identification of new bioactives may serve as a chemophore or pharmacophore to be developed as a drug using Molecular Modeling, Medicinal Chemistry and Bioinformatics approaches. Since, *T. procumbens* is reported to have many pharmacological properties, researchers should try to evaluate their properties using modern technologies.

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AUTHORS CONTRIBUTION

JD supervised and critically reviewed the manuscript apart from literature search and drafting of the manuscript. DK and AT carried out the literature search, written the manuscript. All the authors read and approved the manuscript.

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